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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 10/518,111   | 09/16/2005  | Hans-Uwe Wolf        | SPM-384-A           | 3295             |
| 48980  | 7590        | 11/14/2007           | EXAMINER            |                  |
| YOUNG & BASILE, P.C.<br>3001 WEST BIG BEAVER ROAD<br>SUITE 624<br>TROY, MI 48084 |             |                      | SZNAIDMAN, MARCOS L |                  |
|  |             |                      | ART UNIT            | PAPER NUMBER     |
|  |             |                      | 4173                |                  |
|  |             |                      | NOTIFICATION DATE   | DELIVERY MODE    |
|  |             |                      | 11/14/2007          | ELECTRONIC       |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@youngbasile.com  
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|                              |                                 |                  |
|------------------------------|---------------------------------|------------------|
| <b>Office Action Summary</b> | Application No.                 | Applicant(s)     |
|                              | 10/518,111                      | WOLF ET AL.      |
|                              | Examiner<br>Marcos L. Sznaidman | Art Unit<br>4173 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 12 October 2007.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-17 is/are pending in the application.
  - 4a) Of the above claim(s) 1 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 2-17 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.
 

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>1 page</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|   | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election without traverse of Group II (Claims 2-17) in the reply filed on October 12, 2007 is acknowledged.

Claim 1 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 12, 2007.

On a phone conversation on November 1, 2007 with Attorney Francine B. Nesti, a species election was made for the structures depicted in claim 1, wherein R = methyl, R1 = sulfonic acid, X = methylene and m = 4. However, for the purpose of this office action the species election is withdrawn.

### ***Status of Claims***

Claims 1-17 are currently pending and are the subject of this office action.

Claims 2-17 are presently under examination.

### ***Priority***

The present application is a 371 of PCT/EP03/05830 filed 06/04/2003, and claims priority to foreign application: Germany 102 26 098.2 filed 06/12/2002.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2-17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description Rejection.

Claims 2-17 recite a method of using at least one calixarene as a carrier of active substances in excipient systems.

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention....one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

While the specification describes the use of a calixarene as a carrier of an active substance: acyclovir (Formula VI), and previous art shows a few examples of calixarenes as carriers for active substances; the specification does not convey possession of the entire genus encompassed by active substances.

Given the broad scope of the claimed subject matter, applicant has not provided sufficient written description that would allow the skilled artisan to recognize all the active substances that could be used with calixarenes as a carrier.

Claim 5 and 14 recite a method of using at least one calixarene as a carrier of active substances in excipient systems, wherein the carrier is modified by means of a linker that can be broken down enzymatically and is present as a prodrug.

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive

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means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention....one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

The specification does not provide any example of a linker as to convey possession of the entire genus encompassed by linkers.

Given the broad scope of claimed subject matter, applicant has not provided sufficient written description that would allow the skilled artisan to recognize all the linkers that could be modifying the calixarenes.

Claims 6 and 15 recite a method of using at least one calixarene as a carrier of active substances in excipient systems, wherein the carrier is modified by means of a receptor-analogous group that can be broken down by endocytosis.

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention....one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

The specification does not provide any example of a receptor-analogous group as to convey possession of the entire genus encompassed by receptor-analogous groups.

Given the broad scope of claimed subject matter, applicant has not provided sufficient written description that would allow the skilled artisan to recognize all the receptor-analogous groups that could be modifying the calixarenes.

Claims 8 and 17 recite a method of using at least one calixarene as a carrier of active substances in excipient systems, wherein the active substance is bonded to the calixarene through a spacer, wherein the spacer is one of a nucleotide spacer or a peptide spacer.

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention....one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

The specification does not provide any example of a spacer, wherein the spacer is one of a nucleotide spacer or a peptide spacer, as to convey possession of the entire genus encompassed by nucleotide spacer or a peptide spacer.

Claims 2-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using a calixarene as a carrier of acyclovir (active substance), does not reasonably provide enablement for a method of using all calixarenes as carriers of all active substances. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the predictability or unpredictability of the art; (4) the relative skill of those in the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention, (2) The state of the prior art and (3) the predictability or unpredictability of the art.

The instant invention is directed to a method of using calixarenes as carriers of active substances in excipient systems.

It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and the use of calixarenes as carriers of active substances in excipient systems is considered to be still very unpredictable. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable). Although prior art offers evidence for the use of calixarenes as carriers of active substances, there is no evidence all active substances could be carried by any calixarene. As illustrative of the state of the art, the examiner cites: Millership (Journal of inclusion phenomena and macrocyclic chemistry, 2001, 39: 327-331). Millership teaches that: "there are few publications in the literature that describe the formation of complexes between drug substances and calixarenes and there are no reports of possible uses of calixarenes as pharmaceutical enabling agents" (see page 327, second column, lines 8-11 from the top). Also, due to the size of the internal cavity of these calixarenes there should be a limitation on the size of molecules that would fit in their cavity. For example see Millership on page 330, column 2, lines 5-12: "Shinkai et. al have estimated that the diameter of the upper rim of calyx[4]arenes as 3.8 Armstrong, the calyx[6]arene as 5.0 Armstrong and reported that calyx[8]arene diameter to be difficult to estimate due to conformational fluctuation. So active substances with

bigger diameters than the ones of the calixarenes mentioned before will not fit in their cavities.

This clearly shows that there is not enough evidence in the prior art and in the instant application as to which active substances can be used with which calixarenes as carriers.

(4) The relative skill of those in the art

The relative skill of those in the art is that of an MS or PhD in Chemistry.

5) The breadth of the claims.

The claims are very broad in term of the active substances and the calixarenes that could be used as carriers. There is no mention in the claims of any specific active substance. Regarding calixarenes, claims 9 and 10 depict a very large genus of compounds.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples.

The specification provides only one example of the use of a calixarene as carrier of an active substance: acyclovir. The specification does not provide further guidance for determining which calixarenes can be used as carriers with which active substances.

(8) The quantity of experimentation necessary.

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in determining whether "undue experimentation" is required to make and use the instant invention. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214,218 (CCPA 1976)).

Determining which calixarene to use as a carrier for any particular active substance, would require testing a multitude of calixarenes (qualitatively and quantitatively) for each active substance, then test the pharmacokinetic properties for each mixture in order to determine the best possible combination. This is undue experimentation given the limited guidance and direction provided by applicants.

Therefore, based on the unpredictable nature of the invention and state of the prior art, the lack of guidance and working examples, and the extreme breadth of the claims, one skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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Claims 2-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2-17 provide for the use of "at least one calixarene as a carrier of active substances in excipient systems", but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-3 and 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Millership (Journal of inclusion phenomena and macrocyclic chemistry, 2001, 39: 327-331).

Claims 2-3 and 11-12 recite a method of using calixarenes as a carrier of active substances in excipient systems, wherein the carrier is modified to increase water solubility, in particular by at least one of sulphonic acid groups, carbonic acid groups, amino groups and alcohols (claims 2 and 11).

Millership teaches a method of using 4-sulphonic calyx[4]arene as a carrier for testosterone (active substance)(see title). They also mention investigations into the solution complexation of water soluble calixarenes (referring to calixarenes substituted with sulphonic groups) with testosterone.

The statement in claims 3 and 12: "wherein the carrier is modified to influence pharmacokinetics of the system as second order metabolite, in particular by one of sulphonic groups or glucuronic groups" is an inherent property of the 4-sulphonic calyx[4]arene mentioned in the prior art.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcos L. Sznaidman whose telephone number is 571 270-3498. The examiner can normally be reached on Monday through Friday 9 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MLS  
November 6, 2007

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